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EXAMINER	
SCHMIDT, MARY M	

ART UNIT	PAPER NUMBER
1635	24

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/260,624	OHNISHI, TAKANORI	
	Examiner	Art Unit	
	Mary M. Schmidt	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 March 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-6,8-13 and 15-28* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6,8-13 and 15-28* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *3/5 /03* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Claim Rejections - 35 USC § 112

1. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claims 1-6, 8-13 and 15-28 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are broadly drawn to administration of antisense to RAD51 from any species of organism. The specification as filed taught on page 6 a list of RAD51 homologs.

The specification as filed taught the administration of Rad51 antisense (SEQ ID NOS: 1 and 2) which are the complement of both the human and mouse Rad51 gene (page 15 of the specification, "[t]he two 15-bp antisense oligonucleotides were complementary to a region showing homology between mouse and human sequences"), to mouse 203G glioma cells, and then *ex vivo* administration of said cells to mice in the cisterna magna via injection (page16 of the specification). The mice were further subjected to 6 Gy radiation and the specification taught on page 16 that "[t]he combination of Rad51 antisense oligonucleotides and 6 Gy irradiation

extended the survival time much longer than did either treatment with radiation only or administration of the antisense alone... (Figure 5)." Applicant teaches on page 17 of the specification that "Anatomical and histological studies of dead mice revealed that a growing tumor mass occupied the basal cistern and cisterna magna and severely compressed the brain and spinal cord. In the dead mice treated with antisense oligonucleotide, fluorescence of FITC, which was labeled for the antisense oligonucleotides, was visualized in the tumor cells but a little in the normal tissues of brain and spinal cord."

Applicants work cited below (Ohnishi et al., Biochemical and Biophysical Research Communications 245, 319-324, 1998) clarifies (1) that the mouse 203G glioma cells were administered to the mice prior to the antisense administration to the same site, and (2) that while the dead mice showed growth of gliomas, the mice that survived had not apparent tumors (page 323, col. A).

MPEP 2163 teaches the following conditions for the analysis of the claimed invention at the time the invention was made in view of the teachings of the specification and level of skill in the art at the time the invention was made:

> The claimed invention as a whole may not be adequately described where an invention is described solely in terms of a method of its making coupled with its function and there is no described or art-recognized correlation or relationship between the structure of the invention and its function. A biomolecule sequence described only by a functional characteristic, without any known or disclosed correlation between that function and the structure of the sequence, normally is not a sufficient identifying characteristic for written description purposes, even when accompanied by a method of obtaining the claimed sequence....A lack of written description issue also arises if the knowledge and level of skill in the art would not permit one skilled in the art to immediately envisage the product

> claimed from the disclosed process....Generally, there is an inverse correlation between the level of skill and knowledge in the art and the specificity of disclosure necessary to satisfy the written description requirement....The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice..., reduction to drawings..., or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus.

The claims as filed are drawn to administration of any Rad51 antisense to any species of whole organism. Note the specification as filed contemplates on page 8 that the "individual, or patient, is generally a human subject... the patient may be animal as well." However, since the specification as filed only teaches two antisense to mouse/human Rad51 that function for antisense inhibition of the mouse Rad51 target gene *in vitro* and in mouse, one of skill in the art would not have recognized that Applicant was in possession of a representative number of species of any Rad51 to other animal species as broadly claimed. One of skill in the art would not have been able to readily visualize the sequences of Rad51 antisense to other Rad 51 target genes from other organisms absent the specific sequence structure design criteria having the claimed antisense functions. The description of the instant SEQ ID NOS: 1 and 2 in the specification does not supplement the omitted description of the specific sequence structure of other Rad51 antisense because specific, not general, guidance is what is needed. There is no evidence on the record of a relationship between the structure of the SEQ ID NOS:1 and 2 antisense and the structure of other antisense from humans or other animals that would provide

any reliable information about the structure of other antisense having the claimed functions on the basis of the sequence of SEQ ID NOS: 1 and 2.

The claims thus lack written description for the breath of target RAD51 genes claimed whereby inhibition of RAD51 from any species such as any gene having 80% or greater homology to residues 33-240 from *E. coli* RecA, including RecA and RAD51 homologs from yeast or any mammal (instant specification, page 6, lines 8-25), has the function of inhibiting cell proliferation in any individual as instantly claimed. As cited above, the MPEP teaches that there must be an adequate description of the art-recognized correlation or relationship between the structure of the invention, the antisense to any RAD51 gene, and its function, the inhibition of cell proliferation in any individual. In the instant case, neither the specification as filed nor the prior art teaches this structure-function correlation for a representative number of species of antisense to any RAD51 gene target. Absent this teaching, one of skill in the art would not have recognized that applicant was in possession of the breath of antisense claimed to any RAD51 gene target since one of skill in the art would not have been able to readily envisage the structure of a representative number of antisense to any RAD51 target having the claimed functions in any individual.

3. Claims 1-6, 8-13 and 15-28 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods of use of Rad51 antisense of instant SEQ ID NO:1 and 2 for inhibiting cell proliferation, inducing sensitivity to radiation, inducing sensitivity

to a chemotherapeutic agent, inhibiting the growth of a cancerous cell, prolonging the survival of an individual, or treating cancer via administration of the Rad51 antisense of instant SEQ ID NOS: 1 and 2, does not reasonably provide enablement for use in the claimed methods of any Rad51 antisense as broadly claimed. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and practice the invention commensurate in scope with these claims for the same reasons of record as set forth in the Official actions mailed 11/08/99, 08/01/00, and 08/28/02.

The claims remain drawn to methods treatment of a whole organism such as (1) inhibiting cell proliferation, (2) inducing sensitivity to radiation, (3) inducing sensitivity to a chemotherapeutic agent, (4) inhibiting growth of a cancerous cell, (5) prolonging the survival of an individual, and (6) treating cancer.

There is a high level of unpredictability known in the antisense art for therapeutic, *in vivo* (whole organism) applications. The factors considered barriers to successful delivery of antisense delivery to the organism are: (1) penetration of the plasma membrane of the target cells to reach the target site in the cytoplasm or nucleus, (2) withstanding enzymatic degradation, and (3) the ability to find and bind the target site and simultaneously avoid non-specific binding (see Branch). Note also Ma et al. who teach (on page 167) that "to gain therapeutic advantage using antisense-based technology, ODNs must have certain characteristics. They must be resistant to degradation, internalize efficiently, hybridize in a sequence specific manner with the target nucleic acid, display adequate bioavailability with a favorable pharmacokinetic profile and

be nontoxic." Despite the synthesis of more resilient, nuclease resistant, oligonucleotide backbones and isolated successes with antisense therapy *in vivo*, the majority of designed antisense molecules still face the challenge of successful entry and localization to the intended target and further such that antisense and other effects can routinely be obtained. Flanagan teaches, "oligonucleotides (*in vivo*) are not distributed and internalized equally among organs and tissues.... Unfortunantly, therapeutically important sites such as solid tumors contain very little oligonucleotide following intravenous injections in animals (page 51, column 2)." Ma et al. supports the difficulties of *in vivo* use of ODNs on pages 160-172. Jen et al. further taught that "given the state of the art, it is perhaps not surprising that effective and efficient clinical translation of the antisense strategy has proven elusive. While a number of phase I/II trials employing ONs have been reported..., virtually all have been characterized by a lack of toxicity but only modest clinical effects." (Page 315, col. 2) Green et al. summarizes that "the future of nucleic acid therapeutics using antisense ODNs ultimately depends on overcoming the problems of potency, stability, and toxicity; the complexity of these tasks should now be apparent. Improvements in delivery systems and chemical modifications may lead to safer and more efficacious antisense compounds with improved pharmacokinetics and reduced toxicities." (P. 103, col. B) Note also some of the major outstanding questions that remain in the art taught by Agrawal et al. On page 79, col. 2.

In vitro, antisense specificity to its target may be manipulated by "raising the temperature or changing the ionic strength, manipulations that are commonly used to reduce background

binding in nucleic acid hybridization experiments." (Branch, p. 48) Note also Ma et al. who teach that "*in vitro* subcellular distribution is dependent on the type of ODN modification, cellular system and experimental conditions. ODNs, once internalized, are distributed to a variety of subcellular compartments." (Page 168) Discovery of antisense molecules with "enhanced specificity" *in vivo* requires further experimentation for which no guidance is taught in the specification. Note Branch who teaches the state of the art for designing an antisense which inhibits a target *in vivo:* it "is very difficult to predict what portions of an RNA molecule will be accessible *in vivo*, effective antisense molecules must be found empirically by screening a large number of candidates for their ability to act inside cells (Branch, p.49)." Note Jen et al. who teach that "although mRNA targeting is impeccable in theory, many additional considerations must be taken into account in applying these strategies in living cells including mRNA site selection, drug delivery and intracellular localization of the antisense agent." (Abstract) Bennett et al. further taught that "although the antisense paradigm holds great promise, the field is still in its early stages, and there are a number of key questions that need to be answered and technical hurdles that must be overcome....The key issues concerning this class of chemicals center on whether these compounds have acceptable properties as drugs. These include pharmacokinetic, pharmacological and toxicological properties." (Page 13) As argued above, these issues remain unpredictable in the art for antisense oligonucleotide administration *in vivo*.

One of skill in the art would not accept on its face the successful delivery of antisense other than instant SEQ ID NOS:1 and 2 *in vivo* in view of the lack of guidance in the

specification and the unpredictability in the art. Neither the specification nor technology today teach general guidelines for successful delivery or treatment effects of antisense molecules in whole organisms. Specifically the specification does not teach (1) stability of the antisense molecule *in vivo*, (2)effective delivery to the whole organism and specificity to the target tissues, (3) dosage and toxicity, nor (4) entry of molecule into cell and effective action therein marked by visualization of the desired treatment effects. These key factors are those found to be highly unpredictable in the art as discussed *supra*. The lack of guidance in the specification as filed for these factors would therefore require "trial and error" experimentation beyond which is taught by the specification as filed. The quantity of experimentation would require the *de novo* determination of the unpredictable factors argued above for the breadth of treatments encompassed by the instant claims. Therefore, it would require undue experimentation to practice the invention as claimed.

Response to Arguments

Applicant states on page 6 of the rejection that "the instant specification and the cited art provide examples of the effective use of a diverse group of antisense oligonucleotides. These examples occur in both cultured cell lines and in living tissues. In light of these examples, it is respectfully submitted that stability, dosage and toxicity are not obstacles to the practice of the instant invention. Rather these issues have been, and therefore could also in the future be, resolved employing routine experimentation by one skilled in the art."

However, despite examples in the prior art of successful use of antisense *in vivo*, each antisense must be considered on a case-by-case basis since there are no general guidelines for the development of antisense for use *in vivo* to target genes for specific functions. As argued previously there are layers of unpredictability that compound and must be considered in the design of antisense for use in a whole organism. Those unpredictable factors recited in the previous action preclude the ability of one of skill in the art to design a functional antisense for any hypothetical use in a whole organism since specific guidance is needed for each antisense desired.

Applicant's arguments on page 5 of the response are now moot since the route of administration part of the rejection has been removed.

Claim Rejections - 35 USC § 102

4. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

5. Claims 1-6, 8-12 and 14-28 are rejected under 35 U.S.C. 102(a) as being anticipated by Ohnishi et al. (Biochem. Biophys. Res. Comm. 245:319-324, 1998).

Ohnishi et al. taught the same experiments disclosed in the instant specification (Applicant's own work). They taught administration of instant SEQ ID NOS:1 and 2 to the mouse 203G cells *in vivo* coupled with radiation treatment. They show that the administration of the Rad51 antisense was able to inhibit cell proliferation in the mouse, induce sensitivity to radiation in the mouse, and reduce the cancerous growth of the 203G cells *ex vivo*. They taught direct injection of the antisense oligonucleotides (see pages 320 and 323 especially). Since they taught the sequences of instant SEQ ID NOS:1 and 2 they further anticipated claim 14 drawn to a kit for diagnosing and/or treating cancer comprising a Rad51 antisense molecule. The functional language "diagnosing and/or treating cancer" is not considered to breath further life and meaning into what was an already known composition, a Rad51 antisense. Similarly, the induction of sensitivity to radiation would have been an inherent property of the administered antisense to Rad51. Since a kit is a composition claim, and the composition is the Rad51 antisense, Ohnishi et al. anticipated instant claim 14.

Response to Arguments

Applicant states on page 6 of the response that "[a]s the Ohnishi et al. reference is the Applicant's own work, it is not a proper 102(a) reference."

A statement that Ohnishi et al. is not a proper 102(a0 because it is applicants own work is not convincing since 102(a) is applied when authored by "others". Since the instant application is to Ohnishi alone and the paper is to Ohnishi et al. (four other persons were co-authors of the

Ohnishi et al. reference: Takuyu Taki, Shoju Hiraga, Norio Arita and Takashi Morita), the reference is to "others" and properly a 102(a) is applicable. Since none of these other authors appears as inventor of the instant application, the proper venue to remove a 102(a) in this instance is via a 37 C.F.R. 1.131 declaration (see MPEP 715.01 (c) and 2132.01).

6. Any inquiry concerning this communication or earlier communications from the examiner should be directed to *Mary M. Schmidt*, whose telephone number is (703) 308-4471.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, *John LeGuyader*, may be reached at (703) 308-0447.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group Analyst, *Katrina Turner*, whose telephone number is (703) 305-3413.

M. M. Schmidt
May 28, 2003

JOHN L. LeGUYADER
SUPERVISORY PATENT EXAMINER
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